apparent that the two types of bone change can be present in the same patient, and the availability of specific treatment for osteomalacia makes it important to recognize its presence. Its histological diagnosis depends on the recognition of abnormally large amounts of osteoid tissue: sections of undecalcified bone must be used for this purpose (Ball 1957, Ueckert 1960).

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Dr G Alan Rose
(Department of Medicine Metabolic Unit, General Infirmary at Leeds)

A Study of the Treatment of Osteoporosis with Fluoride Therapy and High Calcium Intake

Introduction

Osteoporosis is the most common of the metabolic bone diseases and yet one about which we understand very little. Although several treatments have been recommended and claimed as causing conversion of calcium balances from negative to positive, no convincing evidence has yet been presented that these treatments lead to increased radio-density of the bones. It is especially curious that high calcium intake has not led to increased radio-density, in view of the very large positive calcium balances claimed from this therapy (Nordin 1962). This discrepancy led Rose (1964*a*) to suggest that technical factors must have rendered the balance data invalid. The calcium balance technique can be greatly improved in accuracy and reproducibility by continuous chromium marking of stools (Hargreaves & Rose 1965); it was thought appropriate to use this improved technique to re-evaluate some of the therapies recommended for osteoporosis. The results of this re-evaluation with respect to fluoride therapy and high calcium intake are now reported.

Patients and Methods

Five patients have been extensively studied. Each patient was admitted on two or more occasions to an air-conditioned metabolic unit for balance studies, using methods previously described (Rose 1964*b*, *c*). Continuous chromium marking was combined with interrupted carmine red marking of stools and all fæcal results have been corrected for chromium recoveries. Balance studies were carried out before treatment, during the first few weeks of treatment and after several months of treatment.

During the first admission each patient was carefully studied to exclude malignancy, endocrinological disturbance, or nutritional abnormality. Previous intakes of calcium and vitamins C and D were evaluated by the unit dietitian. Urinary 17-ketosteroids and either 17-ketogenic steroids or 17-hydroxycorticoids were measured in every case and found to be normal. G M was found to be hypothyroid and this was corrected by L-thyroxine 0·3 mg/day commenced prior to balance studies and continued throughout. No other abnormalities were found. Each patient was shown not to have steatorrhœa or renal failure. Bone biopsy of the iliac crest of H B showed osteoporosis with no other abnormality. Vertebral bodies were obviously rarefied in each case, and each patient except S D showed the

Table 1
Brief details of patients

			Representative plasma values				
Patient	*Age (years)*	*Sex*	*Ca (mg/100 ml)*	*P*	*Alkaline phosphatase (KA units)*	*Vertebral body fractures*	*Clinical notes*
G M	36	F	9·5	4·5	12	++	Bed rest in last six months of pregnancy for pain and swelling of feet. Gross rarefaction of feet, partly reversed but vertebræ then collapsed. Hypothyroidism treated
H B	56	M	9·8	3·3	8	+++	Recurrent vertebral body fractures for nine years
J S	55	M	9·0	3·4	20	++	Recurrent vertebral body fractures for three years
S D	54	M	9·5	3·1	7	–	Recurrent rib fractures for many years
K B	34	F	9·0	2·9	6	++	Severe backache five months after first baby, who was breast fed for six months

irregular vertebral body collapse characteristic of osteoporosis (Rose 1964*d*). Brief details of the patients are given in Table 1.

During the balance studies the basic diet of each patient was such that the calcium and phosphorus contents matched the estimated average normal intake for the particular patient. Calcium supplements were given in the form of effervescent tablets. These tablets were analysed and found to contain exactly the 380 mg of calcium claimed by the manufacturers. Fluoride was given orally, as tablets, each of which contained 30 mg of sodium fluoride. Transient nausea occurred after discharge in 2 patients. They were advised to take the tablets after meals and no further nausea occurred. No other side-effects were noted.

A fluorine balance was carried out on G M while she was on the fluoride therapy. Specimens were sent to Dr W F Waters at the Laboratory of the Government Chemist, London, who kindly carried out the analyses for fluorine.

Results

The balance results are shown in Figs 1–5 and a summary of results in Table 2.

Four patients received fluoride therapy. No changes in renal or hepatic function were observed. Three of the patients showed no significant changes in overall calcium or phosphorus balances. One, S D, showed a slightly lower negative calcium balance on the fluoride than previously. Urinary calcium fell in three cases by 33%, 29% and 17% respectively, and rose in one case by 8·2%.

Table 2
Summary of calcium balances as mg/day

Patient	*Before treatment*	*On sodium fluoride*	*On high calcium intake (follow-up)*
G M	−154	−182	− 3
H B	− 98	− 25	−115
J S	−177		−103
K B	−106	−134	−128
S D	−283	−218	
Mean change		+ 21	+ 35

Fæcal fluorine of G M during the period November 24–29 was 2·5 mg/day and urinary fluorine during the same period was 29 mg/day, giving a positive balance of 23 mg/day.

Four patients (G M, H B, J S and K B) received calcium supplements. Initially negative calcium balances were abolished in each case, while G M developed positive calcium and phosphorus balances. In the follow-up studies, however, none of the patients was in positive calcium balance and the mean improvement was remarkably small at 35 mg/day.

J S received daily calcium gluconate intravenously prior to the oral calcium supplements.

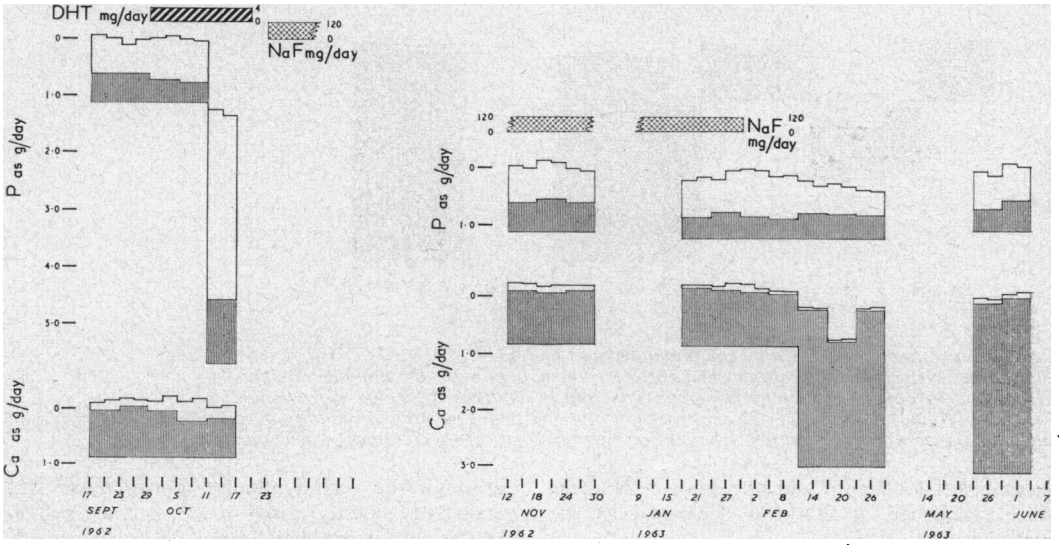

Fig 1 *Balance studies on G M. Here and in Figs 2–5 the charts are constructed using the convention of the Albright school. The base lines represent dietary intake, and on these are built up the fæcal (black) and urinary (white) excretions. Vitamin D changed the partition of calcium between urine and fæces but did not change overall balance. Neutral phosphate supplement (11.10.62–17.10.62) appeared promising but could not be continued. Sodium fluoride (22.10.62–1.2.63) was ineffective. High calcium intake (11.2.63–4.6.63) produced temporary positive calcium and phosporus balances, but these were not present on follow-up*

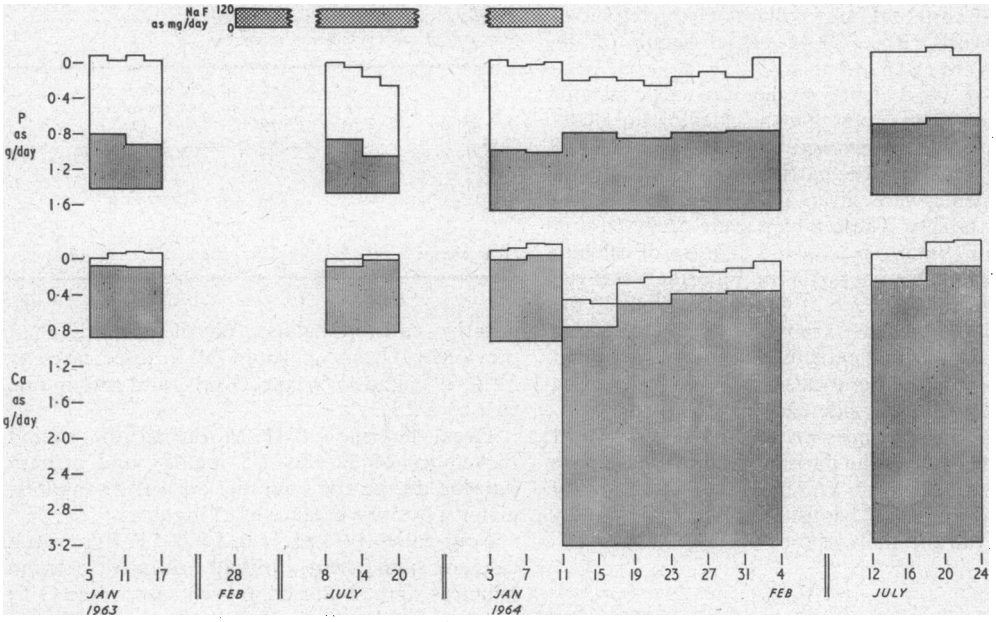

Fig 2 *Balance studies on H B. Sodium fluoride (28.2.63 – 11.1.64) did not change the balances. High calcium intake (11.1.64–24.7.64) brought him into calcium balance for a time, but this improvement was not present six months later*

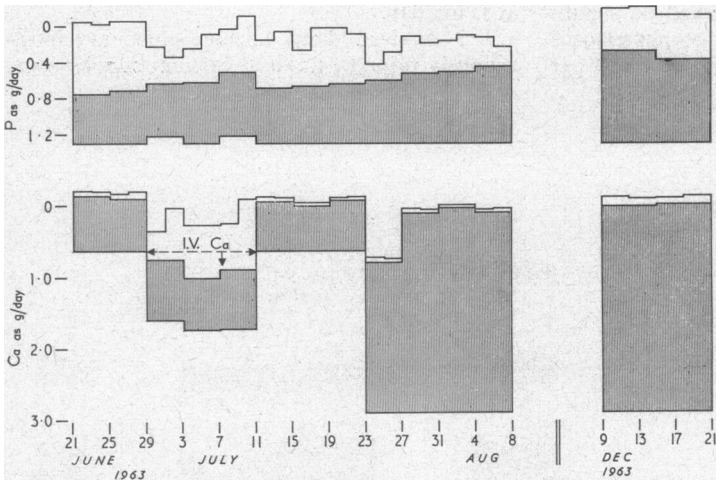

Fig 3 *Balance studies on J S. Daily calcium infusions (29.7.63–11.8.63) led to positive calcium and phosphorus balances but these diminished as the treatment continued. On stopping the infusions there was no loss of the calcium or phosphorus previously retained. With high oral calcium intake (23.8.63–21.12.63) the negative balance ceased at first, but on follow-up four months later, negative calcium balance was again present, though less marked than before treatment was commenced*

Large positive calcium and phosphorus balances were established at first but decreased as the treatment progressed.

Discussion

There was no doubt that each of the patients was suffering from osteoporosis, the usual radiological and biochemical criteria being satisfied. Although the serum alkaline phosphatase was persistently slightly raised in J S, and the reason for this is unexplained, serum flocculation tests and bromsulphthalein excretion tests being normal, the diagnosis was osteoporosis by all other criteria. No endocrine disturbances which could have caused osteoporosis could be found in these patients. Although G M was hypo-

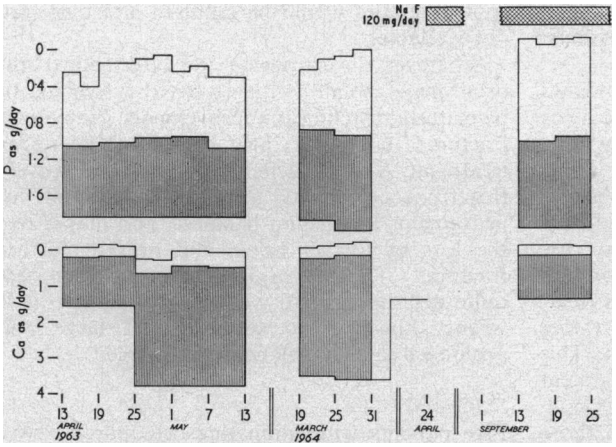

Fig 4 *Balance studies on K B. High calcium intake (25.4.63–2.4.64) made no difference to the calcium balance. Fluoride was also ineffective despite five months of treatment*

thyroid, correction of this did not lead to change in urinary calcium or to a positive calcium balance. Furthermore, hypothyroidism causes osteosclerosis (Royer & Mathieu 1962) rather than osteoporosis. None of these patients can be regarded as senile and the diagnosis of idiopathic osteoporosis seems most appropriate. Admittedly K B and G M presented in association with pregnancy, but there is no evidence that pregnancy is a cause of osteoporosis, and it seems much more likely that the mechanical strains set up by the pregnancies led to the presentations at that time in already osteoporotic individuals.

In this study the patients were treated with fluoride and high calcium intake for long periods of time. Long balance studies, as recommended by Isaksson & Sjögren (1964) were not thought to be necessary since it has been shown (Hargreaves & Rose 1965) that, using continuous chromium marking of stools, two six-day balance periods are sufficient to give highly accurate results. Scrutiny of Figs 1–5 shows that the balance results were indeed very reproducible from one metabolic period to the next while on any given treatment.

Sodium fluoride was remarkably ineffective in all four patients in whom it was tried. The lack of response in calcium balance seemed very surprising in view of the known effect of fluoride in causing ectopic calcification and osteosclerosis (Roholm 1937), and it was therefore thought necessary to measure the fluoride excretion of G M while she was on the fluoride therapy. The results of these measurements were in accordance with the results of Largent & Heyroth (1949), i.e. the fæcal fluoride was very small and the urinary excretion about half of the daily intake and the overall retention was 42% of the dose.

We therefore disagree with the statement of Rich *et al.* (1964) that '. . . fluoride administration results in retention of calcium by subjects with several types of osteoporosis . . .' Examination of the data of Rich *et al.* shows that the improvements in calcium balances which they obtained were not only small, but also of doubtful significance. Thus, of the 4 cases of primary osteoporosis, two showed improvement of only 29 and 14 mg/day respectively. A definite improvement of 213 mg/day of calcium occurred in one patient, but this figure is the mean of four balance periods in which one is quite different from the other three, and it appears that technical difficulties must have occurred. It is therefore suggested that fluoride therapy is ineffective in the treatment of

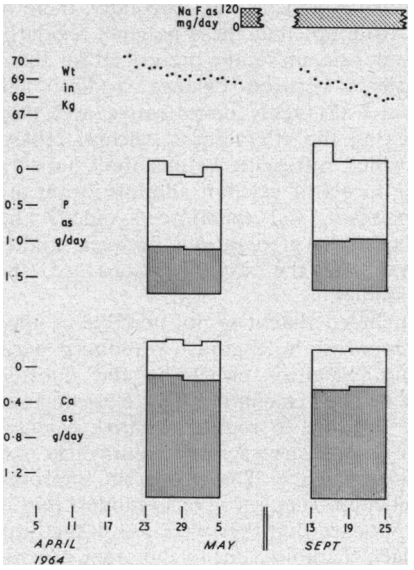

Fig 5 *Balance studies on S D. Fluoride therapy slightly reduced the negative calcium balance after five months of treatment. The slightly worse phosphorus balance was due to his losing weight rather faster during the second study than in the first*

osteoporosis, and should not be recommended for general use since the therapy is hazardous, being a cause of ectopic calcification.

Inspection of Figs 1–5 and of Table 2 shows that results of high calcium intake were nearly as disappointing as those from fluoride therapy. Negative balances were abolished initially, and a definite positive calcium balance established in one case, but the follow-up studies revealed total failure to establish positive balance in any case and a mean gain in calcium balance of only 35 mg/day. There were no side-effects of this treatment, but K B developed urinary calcium values as high as 653 mg/day as an out-patient. This might have led to renal calculi and the treatment was stopped because of this possibility. Again, these results are somewhat different from those reported by others, notably Nordin (1962) and Harrison *et al.* (1961) who claimed large positive calcium balances with high calcium intake. These large positive calcium balances could not have been maintained for long, however, since the authors were unable to demonstrate increased radio-opacity of the bones or soft tissues (*see* Rose 1964*c*). There are at least two possible errors in the earlier work of others which were eliminated in the present work. Firstly, this is the first study of the use of high calcium intake for osteoporosis in which continuous chromium marking of stools has been used throughout. This technique has led to a great increase in reproducibility (Hargreaves & Rose 1965) and is especially required when high calcium intake is under study. Secondly, there is no reason to doubt that these patients regularly took the high calcium intake prescribed for them as out-patients between balance studies. The patients were all highly co-operative and they enjoyed taking the effervescent calcium tablets which provided refreshing drinks three times a day. Other forms of calcium administration are often unpleasant and therefore avoided, and failure to take the preparations between studies could invalidate the interpretations of the follow-up studies.

It is concluded that it is not possible in idiopathic osteoporosis to establish prolonged positive calcium balances either by the fluoride therapy or by high calcium intake. Nevertheless, it may be possible to reduce negative calcium balances or even arrest them completely for short periods of time. The long-term improvements in calcium balances were so modest that it could be supposed that they were not in fact due to the specific therapies, but to the other general measures used. Each patient was advised to be as active as his circumstances would permit so as to prevent any secondary immobilization osteoporosis. This alone might have had significant effects. To confirm or disprove this supposition, control studies would be required and these are not available.

Whatever the causes of the biochemical improvements, small as they were, they seemed to be matched by clinical improvements. No patient fractured bones or lost height while under treatment. A high calcium intake seems relatively free from side-effects, may lead to modest improvements in calcium balances, and may arrest the loss of further bone, and prevent further fractures. These marginal improvements are quite definitely worth while to the patient. It is wrong, however, to suppose that large and prolonged calcium balances are achieved.

Summary

Five patients with idiopathic osteoporosis have had repeated calcium and phosphorus balance studies in an attempt to demonstrate the immediate and long-term effects of fluoride therapy and high calcium intake. Continuous chromium marking of stools was used throughout to improve the accuracy of the balances.

Fluoride was found not significantly effective both immediately and after several months of therapy.

High calcium intake led to temporary improvements in calcium balance, but after several months of the treatment the calcium balances were almost the same as before treatment.

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